IN-DEPTH REVIEW

Neutrophil and Monocyte Alterations in Chronic Dialysis Patients

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● Chronic renal failure patients maintained on dialysis have an increased risk for infection. This article summarizes research that has been done on the function of neutrophils (PMNs) and monocytes from chronic hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients. The studies involving the HD patients showed that there is a decreased PMN in vitro chemotactic response, decreased C5a receptors on both PMNs and monocytes, and decreased oxidative metabolic responses of PMNs and monocytes to the chemotactic stimuli C5a and formyl-met-leu-phe (fMLP), but not to nonchemotactic factors. The results of studies involving phagocytosis have been conflicting and are discussed in this paper. Due to the basic principles of peritoneal dialysis, this treatment approach depletes the peritoneum of phagocytic cells, adversely affects the function of peritoneal WBCs, dilutes the existing opsonins, and alters the physiologic environment of the peritoneal cavity. Studies of peripheral PMN and monocyte function in CAPD patients have shown that, similar to HD patients, they also have decreased C5a receptors and decreased oxidative metabolic responses to the chemotactic factors C5a and fMLP. Although the factors contributing to the risk of infection in chronic dialysis patients are multifaceted, there are definitely alterations in PMN and monocyte function.
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INDEX WORDS: Dialysis; hemodialysis; peritoneal dialysis; neutrophil; monocyte; chemotactic factors; infection.

ALTHOUGH IT HAS BEEN known for many years that patients with chronic renal failure (CRF) have an increased susceptibility to infection, the mechanisms involved in this increased risk for infection are only partially understood. The purpose of this article is to summarize what is known about neutrophil (PMN) and monocyte function in CRF patients, primarily those maintained on hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD).

In 1968, Montgomerie et al reported a 60% incidence of infection in hospitalized CRF patients and noted that infection was a major cause of death in 38% of these patients.[1] Although the incidence has decreased, infection continues to be a common cause of morbidity and death among chronic dialysis patients.[2] The percentage of reported deaths due to infections varies among HD populations (Table 1).

Bacteria account for a majority of the infections in HD patients with Staphylococcus aureus the most common causative organism followed closely by Staphylococcus epidermidis and Escherichia coli.[3,5,10] The most common sites of bacterial infections include vascular access sites, lungs, and urinary tract.[3,10]

CAPD is increasingly being used to treat patients with CRF. Although many advances have been made in CAPD during the past 10 years, bacterial peritonitis remains the major complication.

Table 1. Percentage of Deaths in Chronic HD Patients Due to Infection

Deaths (%)	No. of Patients	Length of Observation (yr)	Ref. No.
19.8	445	4	3
19.8	1014	11	4
24.0	333		5
35.7	24	14	6
13.1	1453	6	7
15.7	83	10	8
14.9	373	10	9

Peritonitis will occur at least once in 60% of CAPD patients with an overall rate of 1.4 episodes a year.[11] In addition to peritonitis, CAPD patients have a high incidence of exit-site and tunnel infections that frequently lead to peritonitis. In CAPD, the origin of infection is most often exogenous with S epidermidis and S aureus the most common infecting organisms.[11,12] Although the mortality rate due to peritonitis is actually low,[11] frequent bouts of peritonitis often necessitate the termination of CAPD.

OVERVIEW OF PHAGOCYTIC CELL FUNCTION

The primary purpose of PMNs and monocytes is to defend against injury and infection. These cells are mobilized from circulation to the site of injury by a process known as chemotaxis, which is the migration of WBCs along a concentration gradient of chemoattractant to the site of injury or infection. The interaction of the WBC and the chemotactic factor is mediated through specific receptors on the WBC surface. Chemotactic factors also elicit numerous other responses in PMNs and monocytes, including aggregation (adherence of cells to each other), increased adherence, enzyme release, degranulation, and oxidative metabolism. Many of the same metabolic and degranulating responses occur during phagocytosis. When a microorganism or insoluble immune complexes are phagocytized, the cell undergoes a burst in O_2 consumption followed by the conversion of molecular O_2 to extremely toxic O_2 radicals (a reaction referred to as oxidative metabolism). The toxic O_2 derivatives, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), and single oxygen ($^1O_2$), are directly involved in the killing of microorganisms, tissue damage, and cytotoxic activity. H_2O_2 is one of the most important intermediates in mediating bactericidal activity and has been shown to interact with halide ions

(usually chloride) using myeloperoxidase (MPO), released from intracellular PMN granules, as a catalyst to form hypochlorous acid, which also has potent antimicrobial activity.

The studies described in this review involve the determination of many different WBC functions, including chemotaxis, phagocytosis, and various components of oxidative metabolism. Methodologic techniques are described where appropriate, especially to explain differences in findings.

WBC FUNCTION IN CHRONIC HEMODIALYSIS PATIENTS

Changes in WBC Counts During HD

Profound leukopenia (primarily limited to PMNs and monocytes) occurs in patients within 30 minutes of being on HD[13-17] (Fig 1). The leukopenia is the result of sequestration of leukocytes in the pulmonary capillary circulation. Interaction of the dialyzer membrane with the patient's blood causes activation of the alternate pathway of complement to generate the biologically active complement component C5a.[18] Activation of PMNs and monocytes with C5a results in aggregation of PMNs and increased adherence of these cells to endothelial surfaces of capillaries. This activation leads to pulmonary leukostasis as a result of margination of PMNs and monocytes in the microvasculature of the lungs. These C5a-mediated changes are contributing factors in the acute pulmonary pathologic changes of leukostasis found during the first 30 minutes to one hour after dialysis is initiated.[16,19,20] Within one to two hours of initiating HD, there is rebound leukocytosis that
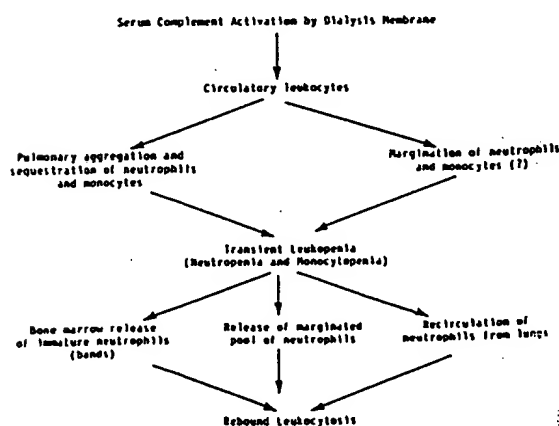

Fig 1. Model for dialysis-induced leukopenia and leukocytosis.

can be attributed to either return of the WBCs into circulation from the lungs[15] and/or bone marrow release of immature (band) PMNs into circulation.[15,21-23]

There have been many studies involving the relationship between different dialysis membranes and the extent of complement activation and/or degree of leukopenia.[24-26] The most common membranes studied have been different cellulose products, including cupraammonium cellulose, regenerated cellulose, and cellulose acetate. In addition, noncellulose membranes such as polycarbonate, polysulfone, polymethylmethacrylate, and polyacrylonitrile have also been investigated. These studies have shown that cellulose membranes have the most and noncellulose membranes the least potential to cause complement activation and neutropenia.[27-35] In addition, the average predialysis WBC count of patients using cellulose dialyzers was lower than when the same patients were treated with polyacrylonitrile dialyzers.[31,32] Other studies have shown profound activation of the complement system by the alternate pathway (as indicated by high plasma C3a levels and an absence of C4a elevation) with cupraammonium cellulose membranes, moderate activation with cellulose acetate membranes, and minimal activation with polyacrylonitrile membranes.[32,36,37]

Granulocyte Function

A summary of granulocyte function is presented in Table 2.

Alterations in the PMN chemotactic response. A consistent finding in in vitro studies of patients on HD is a defect in chemotaxis. Baum et al[65] demonstrated an improvement of depressed in vitro chemotactic responsiveness after the initiation of maintenance HD treatment in uremic patients. However, there is more evidence that HD does not improve the leukocyte function and may actually have a detrimental effect on PMNs. Using an in vitro model for HD, Henderson et al[66] showed that contact of normal whole blood pumped through cellulose membranes depressed the chemotactic properties of normal PMNs. This defect became more progressive with the duration of HD. Greene et al[39] showed a depressed in vitro chemotactic response of PMNs from HD patients to chemotactic factor from *E coli* bacteria that was more profound than in patients on conservative treatment. They also demonstrated a progressive deterioration in the PMN chemotactic response with multiple HD treatments. These findings were confirmed by Bjorksten et al[40] who found a depressed response of PMNs from HD-treated patients to *E coli* and zymosan-activated serum. In addition, it was found that impaired chemotactic responsiveness could develop after several dialyses in uremic patients whose initial chemotactic response was normal.[39,40] These studies indicate that possible harmful effects of HD on the chemotactic response of PMNs cannot be excluded.

The relationship between the defect in PMN chemotaxis and increased susceptibility to infection in HD patients remains speculative. Patients with defective PMN chemotaxis are known to have an increased frequency of bacterial infections.[67] In dialysis patients, however, many other factors such as poor nutrition and vascular access sites are also major contributing factors to infection.[41,44] Nevertheless, the implication is that a chemotactic defect certainly decreases the capacity of these patients to defend against bacterial infections.

Chemotactic receptors. A possible mechanism for the decreased chemotactic response in HD patients is an alteration in the chemotactic receptors. This question was addressed in our studies where the binding of several fluorescent chemotactic factors to PMNs and monocytes from these patients were assessed.[49,50] The results of these studies indicated there was a significant decrease in the percentage of PMNs capable of binding C5a, but no difference in the binding of fluorescent formyl-methionyl-leucyl-phenylalanyl-lysine (fMLPL) as compared to controls.

As stated earlier, during the HD procedure, there is continual generation of C5a due to membrane-induced activation of the complement system. Chenoweth et al[37] found that the predialysis plasma C5a levels in HD patients were higher than in controls. Thus, these patients are exposed to high concentrations of C5a that may modulate the number of available C5a receptors on PMNs and monocytes. It is possible, therefore, to explain the decreased responsiveness of the PMNs and monocytes from the HD patients due to C5a down-regulation of this receptor secondary to continual generation of C5a from complement activation by the HD membrane. This explanation is supported by other studies involving deactivation of chemotactic-responsive cells.[68-75] These studies showed

Table 2. Granulocyte Function in Chronic HD Patients

Parameters	Findings	Factor/Stimulus	Ref. No.
PMN chemotaxis	↓	Bacterial endotoxin-activated serum	38
	↓	E coli bacterial factor	39
	↓	E coli, zymosan-activated serum	40, 46
	↓	Zymosan-activated plasma	41, 42, 47
	↓	Zymosan-activated plasma, cellophane-incubated plasma, supernatants from E coli cultures	43
	↓	Immune complexes, whole E coli bacteria	44
	↓	Pooled inactivated human serum, casein, zymosan-activated autologous serum	45
	↓	C5a, fMLP	48
	Normal	S aureus	45
	Normal	fMLP	41
Chemotactic receptors	↓	C5a	49, 50
	Normal	Casein, fMLP	49, 50
	Normal	fMLP	22
Fc receptors	Normal		49-51
PMN phagocytosis	Normal		44, 46, 52-56
	↓		38, 45, 54, 57-59
Oxidative metabolism			
CL response	↑	Resting levels	60
	↓	PMA	60
	Normal	Zymosan	46
Superoxide generation	Normal	PMA	48, 60
	↓	C5a, fMLP	48
H2O2 production	↑	PMA	22
	Normal	PMA	48
	↓	C5a, fMLP	48
Oxygen consumption	↓	PMA, opsonized zymosan	47
Glucose uptake	↓	PMA, opsonized zymosan	47
Lactate production	↓	PMA, opsonized zymosan	47
HMPS activity	↑	PMA, opsonized zymosan	47
MPO release	Normal	PMA	48
	↓	C5a, fMLP	48
PMN reduction of NBT	Normal	Resting cells	44, 60
	↓	Phagocytizing cells	44
	↓	Resting cells	58, 61
PMN adherence	Normal		51, 55, 62, 63
PMN bactericidal capacity	Normal	S aureus	38, 45, 46, 55
	Normal	S aureus, E coli, Bacteroides fragilis	44
	↓	S aureus, E coli	54
Opsonization and bactericidal activity of serum	Normal	S aureus, C albicans	38, 52, 55
	↓	E coli, S aureus	59
	↑	Bacillus subtilis	59
	↓	Proteus rettgeri	64

Abbreviations: HMPS, hexose monophosphate shunt; NBT, nitroblue tetrazolium.

that preexposure of PMNs to chemotactic factor resulted in a decrease in the number of receptors available for subsequent chemotactic factor binding.

The characteristics of chemotactically deactivated cells have not been fully evaluated nor is the clinical significance of chemotactic deactivation known. In a group of studies by Solomkin et al[76-79] involving patients with trauma and infection, possible mechanisms for abnormal chemotactic and bactricidal ability of PMNs were investigated. They found decreased in vitro chemotactic responsiveness of PMNs to both fMLP and C5a, and receptor analysis showed a specific loss of C5a binding and normal or enhanced fMLP binding. Plasma levels of C3a were elevated as compared to

the controls, and there was a linear relationship between plasma C3a levels and decreased in vitro PMN chemotactic response to C5a and fMLP, indicating nonspecific deactivation. Similar findings were also found in patients with adult respiratory distress syndrome (ARDS).[80,81] In two different studies involving these patients, plasma C3a levels were increased and there was a profound depression in PMN chemotaxis to fMLP and a fourfold elevation of lysosomal enzyme release relative to PMNs from healthy controls.[80,81]

These studies involving patients with trauma, infection, and ARDS indicate that deactivation and degranulation in response to high circulating levels of complement components are at least partially responsible for the abnormalities in PMNs obtained from these patient groups. It may be that similar results of complement activation occur in HD patients.

Oxidative metabolism. In addition to mobilizing PMN to the site of injury or infection, chemotactic factors also stimulate PMN and monocyte oxidative metabolism. There have been a limited number of studies that have investigated the oxidative metabolism of PMNs from HD patients. In our previous studies,[48] chemotactic-factor–stimulated oxidative responses and degranulation were studied using superoxide anion generation, H_2O_2 production, and MPO release to measure the response of PMNs or monocytes. The ability of PMNs and monocytes from HD patients to produce superoxide anion and H_2O_2 in response to C5a and fMLP was significantly lower than normal controls. Similar results were obtained with MPO release from PMNs. When either PMNs or monocytes were stimulated with phorbol myristate acetate (PMA), however, no difference between the patients and controls was observed. These data suggest that the abnormal responses of PMNs are restricted to C5a and fMLP. Although the reduction in response to C5a is easily explained by a loss of C5a receptors, the abnormal response to fMLP is not totally understood.

Modulation of chemotactic factor receptors in HD patients may be a contributing factor in these patients' increased risk to infection by preventing the normal function of C5a in an inflammatory response. The observed reduction of chemotactic-factor–stimulated superoxide generation, H_2O_2 production, and MPO release in response to C5a and fMLP may be an important part of decreased resistance to infection, since the production of

oxygen radicals and the release of MPO are critical to the killing of microorganisms.

Chemiluminescence (CL), a measurement of stimulated PMN to emit light, is frequently used to assess the oxidative burst in PMNs. Using both normal healthy controls and HD patients, Ritchey et al[60] found that the resting values of CL from HD patients' PMNs in autologous serum were higher than control PMNs. The response of patients' PMNs to stimulation with PMA exhibited significantly less of an increase over resting values than did control cells. Cross-incubation studies were performed to evaluate the effects of serum from HD patients on CL. These demonstrated that the resting CL was significantly lower with HD cells in control serum when compared with HD cells in autologous serum. Light emission from patients' PMN in response to PMA, however, was similar in autologous and control serum. Cross-incubation studies with control PMN in either control or patient serum indicated that the resting values of light emission were significantly elevated in the presence of patient serum. There was no difference, however, in PMA-stimulated CL of PMNs placed in either autologous or patient serum. In summary, these results show that the resting CL from PMNs of HD patients is elevated. This is likely due to factors present in their serum that trigger a CL response. In addition, there is a reduced CL response to PMA in the predialysis period. Comparison of postdialysis with predialysis PMN show that the resting levels of CL are significantly less postdialysis, but the PMA-stimulated values are not significantly different.

A variety of PMN metabolic responses in HD patients studied by Briggs et al[47] used opsonized zymosan or PMA as stimuli. The results, which were consistent using either stimuli, showed that there was significant impairment of stimulated oxygen consumption, glucose uptake, and lactate production. There was no difference in the resting rates of oxygen consumption between patient and control groups. These results suggest that PMNs from HD patients have significant alterations in their glucose and oxygen metabolism as well as impaired intracellular energy production and availability. These alterations could contribute to granulocyte dysfunction and make these patients more vulnerable to infection.

Phagocytosis. The results of studies involving phagocytosis by PMNs obtained from HD patients have been conflicting. These are briefly summa-

Table 3. Phagocytic Ability of PMNs
From HD Patients' Phagocytic System

Phagocytic Uptake	Particles	Serum/Plasma	Ref. No.
Normal	Yeast	Patient serum	54
Normal	S aureus	Patient or normal serum	55
Normal	S aureus C albicans	Patient or normal serum	52
Normal	S aureus E coli Bacteroides fragilis	Patient or normal serum	44
Normal	C albicans	Patient plasma	53
Normal	S aureus	Not indicated	46
Normal	Latex particle	Whole blood	56
↓	Latex particles	Not present	57
↓	Bacillus substilis	Patient or normal serum	59
↓	C albicans	Patient or normal serum	38
↓	S aureus	Patient serum	54
↓	E coli	Patient serum	54
↓	S aureus	Normal serum	58
↓	Salmonella typhimurium		
↓	S epidermidis	Patient or normal serum	45

rized in Table 2 and analyzed in more detail in Table 3. Different patient populations have been studied with little data concerning the duration of dialysis treatment to make proper comparisons between the studies. Neither do these studies give specific information on which opsonins are involved in serum- or plasma-incubated particles. Analysis of these studies shows a wide variety of methodologies and, even in the same assay systems, there are reported differences using the same bacterial strains or *Candida albicans*. The results of studies showing normal phagocytic activity were done using patient plasma or serum; therefore suggesting the exclusion of a possible depressive effect of the uremic serum on phagocytic ability. In general, it is difficult to derive any firm conclusions from this wide variety of findings.

Adherence. Granulocytic adherence is an important step in the chemotactic response because it precedes diapedesis of the cells through the vessel wall and migration into the tissues. It has been shown that adherence greatly enhances the oxidative and degranulation responses of PMNs to chemoattractants.[82,83] Adherence assays on CRF patients have produced variable results. Lespier-Dexter et al[63] and Abrutyn et al[55] found normal adherence in uremic patients not on dialy-

sis. Lespier-Dexter et al, however, found that HD patients had a significant impairment in PMN adherence, and this reduction became progressive during the HD procedure but returned toward baseline values at the end of the procedure. Spagnuolo et al[51] found normal adherence in the predialysis period, but a decreased response at 15 minutes with return to normal levels by the end of dialysis. Although it is difficult to make any conclusions from these studies, it seems that if there is an adherence defect, it is due to HD and not a result of the disease process.

Monocyte Function

There is a scarcity of literature related to monocyte function in CRF patients. In many ways these cells' chemotactic, phagocytic, and bactericidal mechanisms are similar to PMNs. Thus, it would seem possible that many of the PMN alterations discussed in the previous section could also be found in monocytes.

Using the Rebuck skin window technique, Hanicki et al[84] demonstrated a decreased number of monocytes that migrated to the test site compared to the controls. Using the same technique, Ringoir et al[85] showed no difference in the migration of monocytes of the HD patients compared to controls. The former study used dinitrochlorobenzene (DNCB) as a stimulant and the latter a 1-cm incision in the skin. Using the same skin window technique, Ringoir et al measured the phagocytic activities (ingestion of carbon particles) of monocytes from HD patients, dividing them into two groups according to having received more or less than 4 months of HD. The phagocytic activity in patients with <4 months of HD had impaired phagocytosis compared to controls. In contrast, patients on >4 months of HD had a significantly improved phagocytic index and their results were not significantly different than control values.

Similar to our results with PMNs, monocytes from HD patients showed decreased availability of C5a receptors. This contrasted with no difference between controls and HD patients in the binding of casein or fMLP.[49,50] Chemotactic-factor–mediated functional responses in monocytes as assessed by superoxide anion generation, H_2O_2 production, and MPO release were decreased in response to C5a and fMLP in HD patients as compared to controls, but no difference was found when PMA was used as a stimulus. The same conclusions can be

derived as for PMNs in that the reduction in C5a receptors and decreased responsiveness of monocytes to chemotactic factors may contribute to an increased risk of infection in HD patients.

The metabolic activation of monocytes as determined by attachment, spreading, and reduction of nitroblue tetrazolium has been shown to be significantly enhanced.[86] This finding was interpreted as a sign of nonspecific cellular activation. However, in the same study, the in vitro phagocytic capacity of monocytes for IgG-coated RBC was shown to be impaired.

Intradialysis Studies on WBC Function

Some studies have shown that the PMNs that remain in the peripheral circulation during the leukopenic period associated with HD are functionally defective as compared to the same patient's predialysis PMNs. These studies have shown (1) diminished CL response,[22,87] (2) decreased H_2O_2 secretion,[22] (3) abnormal chemotactic response,[21,41] (4) fewer surface receptors for a formylated peptide,[22] (5) decreased number of circulating Fc-receptor–bearing PMNs,[21,51] (6) defective aggregation response,[21,41,51] and (7) diminished PMN adherence.[21,51]

Altered oxidative metabolic responses of intradialysis PMNs were found in two different studies. Wissow et al[87] reported a decrease in light emission among PMNs harvested 30 minutes after the initiation of HD in response to S aureus opsonized with either predialysis or dialyzed serum. These findings were verified by Cohen et al[22] who found a significant decrease in CL in intradialysis cells harvested at 15 minutes. This decrease occurred whether cells were responding to particle ingestion (opsonized zymosan) or soluble stimuli (PMA or fMLP). No attempt was made in either of these studies to compare HD patients in the predialysis period to normal controls. Additional defects in oxidative metabolism were seen in two HD patients studied by Cohen et al[22] who found decreased H_2O_2 release by intradialysis PMNs in response to PMA as compared to the same patients' predialysis PMNs.

Other functional responses that have been shown to be defective in the intradialysis period include chemotaxis, aggregation, and adherence. Abnormal in vitro PMN chemotactic response to E coli endotoxin-activated serum was found in cells harvested at 20 minutes into dialysis[21] and to C5a des

arg in cells harvested at 120 minutes into dialysis.[41] Impaired aggregation of PMNs has been found in cells harvested (1) at 15 minutes intradialysis and using fMLP as a stimulus,[51] (2) at 20 minutes intradialysis and using C5a des arg as a stimulus,[21] and (3) at 120 minutes intradialysis and using C5a des arg or fMLP as a stimulus. Decreased in vitro adherence of PMN to plastic surfaces has been found with two adherence-augmenting factors, fMLP and endotoxin from E coli, using cells harvested at 15 minutes intradialysis,[40] and impaired adherence without the use of stimulating factors was also found at 20 minutes intradialysis.[21]

Our study on the analysis of chemotactic factor receptors throughout the HD procedure[88] has shown no significant difference in the percentage of PMNs or monocytes binding C5a, casein, or fMLPL at four different time intervals (0, 1/2, 2, and 4 hours). At the 15 to 30 minute intradialysis period, previous investigators have shown 27% fewer PMN receptors for a formylated peptide (N-formyl-Nle-Leu-Phe-Nle-Tyr-Lys)[22] and a decreased number of circulating Fc-receptor–bearing PMNS,[21,51] as compared to the same patients' PMNs before the dialysis procedure was initiated. These three studies used the cell pellet from Ficoll-Hypaque (Pharmacia, Piscataway, NJ) separated blood. In a previous study,[89] we have shown that after the initiation of HD, Ficoll-Hypaque preparation of PMNs from blood samples is not an appropriate method to analyze PMN function since PMNs respond to C5a with alterations in cell density and are lost from the cell pellet and appear with the mononuclear cells. Thus, the cell pellets of the previous studies would not be representative of the total population of PMNs. Previous postulation that there is a defective population of PMNs in circulation during the dialysis procedure may, in part, reflect the method of cell separation. Many of the studies mentioned previously[21,22,41,51,58,90] used PMNs recovered in the cell pellet following Ficoll-Hypaque separation of blood obtained during the intradialysis period. Based on our results, these cells would represent the unresponsive PMNs selectively isolated by the Ficoll-Hypaque procedure. Thus, interpretation of the previous finding is complicated by the procedures used to isolated PMNs, and the resultant data may not be representative of the entire PMN population.

In addition to HD, other conditions and diseases

in patients that involve in vivo chemotactic factor activation include autoimmune disease (eg, systemic lupus erythematosus), infectious diseases, cardiopulmonary bypass, major burns, diabetes mellitus, and ARDS. Our results indicate that caution should be taken in procedures used to isolate and evaluate PMN functions or responses in such patients where complement activation may have occurred.

WBC FUNCTION IN CHRONIC PERITONEAL DIALYSIS PATIENTS

Many factors contribute to the pathogenesis of peritonitis in CAPD patients. The most obvious is exogenous contamination from the skin disruption caused by the indwelling catheter. In addition, there is potential contamination from tubing and bag exchanges. Whether CAPD induces abnormalities in the normal host defense mechanisms of the peritoneal cavity has only recently been studied. In general, there is a scarcity of literature on WBC function in patients on chronic PD.

Due to the basic principles of peritoneal dialysis, patients almost always have large quantities of fluid in the peritoneal cavity. The changing of the fluid at least four times a day depletes the peritoneum of phagocytic cells and alters the physiologic environment. Commercial dialysis fluids have an initial pH as low as 5.2 with osmotic concentrations ranging from 275 to 479 mosm/kg (normal serum is 285 to 295 mosm/kg). In addition, the large fluid volume (usually 2 L) disrupts the normal intraperitoneal circulation, which normally contains <50 mL of fluid.

In CAPD patients, inflammation of the peritoneal cavity is usually contained locally without a systemic response. In contrast to surgical patients with peritonitis, peripheral leukocytosis is generally not seen in CAPD patients with bacterial peritonitis unless it is accompanied by extraperitoneal infection.[91,92] Vas et al[92] suggested that peritoneal dialysis interferes with the normal mechanisms of lymphatic absorption and drainage, which impedes passage of the pathogens into the systemic circulation. This defect is most likely a result of the mechanical factors associated with the instillation of large fluid volumes into the peritoneal cavity. Normally, the peritoneal lymphatics are important in the removal of bacteria from the peritoneal cavity. The consequences of the altered lymphatic function in CAPD patients are really not known.

Host Defenses in the Peritoneal Cavity

Most of the studies of WBC function in CAPD patients have focused on host defense mechanisms of the peritoneal cavity and the effect of CAPD. Studies on the cellular composition of peritoneal effluent show that the cellular response of the peritoneal cavity to long-term peritoneal dialysis is largely monocytic. Peritonitis is accompanied by a tremendous increase in cellularity primarily due to an increase in PMNs.[93,95] Normal effluents have up to 50 WBC/μL, and in the presence of peritonitis, 100 to several thousand WBC/μL can be found.[96] Following adequate treatment of peritonitis, the WBC count returns to normal and the cellular response becomes monocytic again.

Commercial dialysis solutions adversely affect both the PMNs and monocytes. The function of peritoneal macrophages may be temporarily compromised during the period following infusion of the dialysate solution. This adverse effect is probably due to the low pH and high osmolality of the fluid. Goldstein et al[97] found that all mononuclear cells (peripheral blood and peritoneal) that were incubated in 100%, 50%, or 25% dialysate (pH 5.5, osmolality 310 to 580 mosm/kg) showed complete loss of viability. Adjusting the pH to 7.4 did not alter this loss of viability, implying that the hypertonic solutions were the primary cause of cell death. Another study showed that the dialysate, after a four-hour intraperitoneal dwell period, did not impair lymphocyte viability or lymphocyte transformation in response to phytohemagglutinin (PHA).[12] Granulocyte function as determined by nitroblue tetrazolium reduction following in vitro exposure of the patients' own cells or normal control cells to dialysate was also unaffected. This same study showed that fresh dialysate killed 99% of the lymphocytes after a three-hour incubation in 4.25% dextrose solution. Using samples removed at intervals from the peritoneal cavity, another study showed all samples of removed dialysate fluid suppressed the activity of peripheral WBC as measured by CL, phagocytosis, and bacterial killing.[98] Peripheral blood leukocytes were suppressed 98.8% in their CL response following incubation in fresh dialysate solutions. Within the peritoneal cavity, the pH of the dialysate solution was adjusted to noninhibitory levels within 30 minutes, but the osmolality changes were less rapid and remained at inhibitory levels for fluids of 4.25% dextrose concentrations for the

five-hour period studied. This first 30 minutes following infusion of the dialysate solution is a critical period since it is the time when the host defenses must cope with a large influx of bacteria. The results of these three studies imply that phagocytic cells and lymphocytes may be seriously damaged before the dialysate solution approaches isotonicity and physiologic pH.

A study investigating bacterial growth in fresh and spent dialysate showed that S aureus and S epidermidis did not survive in fresh dialysate, but grew rapidly in peritoneal effluents obtained from patients after the dwell time. This finding suggests that these fluids are modified during the intraperitoneal dwell time to become suitable media for bacterial growth. In contrast, E coli grew well in both pre- and postdialysis peritoneal fluid. Thus, the survival of bacteria contaminating the peritoneal cavity is dependent on the microbial species as well as composition of the peritoneal cavity fluid at the time of their entry. Further experiments

showed that peritoneal macrophages, when present in sufficient numbers (at least 10^6/mL), were able to suppress bacterial growth.[99] Normally, however, there would only be approximately 1×10^4 to 5×10^4 cells/mL.[100]

The studies that have been done to analyze host defense mechanisms in CAPD patients are summarized in Table 4. Using radiolabeled microorganisms and either fresh or heated normal serum for opsonization, Verbrugh et al[100] showed that peritoneal macrophages phagocytized opsonized S aureus and S epidermidis as efficiently as PMNs from normal donors. These cells were also able to phagocytize nonopsonized S aureus. Phagocytosis of E coli required the presence of heat-labile serum factors (probably complement-related), since 56°C-heated serum was not opsonic for this strain. Using similar opsonization techniques as in their phagocytosis assay, this same study showed that peritoneal macrophages killed these three same strains of bacteria as efficiently

Table 4. Host Defense Mechanisms in CAPD Patients

Parameter	Finding	Factor Stimulus	Ref. No.
Peritoneal monocytes/macrophages			
Phagocytic capacity	Normal	S epidermidis, E coli, * S aureus	100
Bactericidal ability	Normal	S aureus, E coli, S epidermidis	97, 100
	↓	C albicans	102
CL (compared to normal PMN)	↓	Zymosan, PMA	100
Chemotactic response (in vitro)	↑	fMLP	97
H₂O₂ generation	Normal	PMA	97
Opsonic activity of peritoneal fluid	↓	C3, IgG	100, 101
Peripheral blood monocytes			
Chemotactic response (in vitro)	↑	fMLP	97
Chemotactic receptors	Normal	fMLP, casein	49, 50
	↓	C5a	49, 50
Bactericidal ability	Normal	S aureus, E coli	97
H₂O₂ generation	Normal	PMA	48, 97
	↓	C5a, fMLP	48
Superoxide production	Normal	PMA	48
	↓	C5a, fMLP	48
Fc receptors	Normal		49, 50
Peripheral neutrophils			
Chemotactic receptors	Normal	fMLP, casein	49, 50
	↓	C5a	49, 50
Chemotactic response (in vitro)	↓	C5a, fMLP	48
Superoxide anion production	Normal	PMA	48
	↓	C5a, fMLP	48
H₂O₂ generation	Normal	PMA	48
	↓	C5a, fMLP	48
MPO release	Normal	PMA	48
	↓	C5a, fMLP	48

*See text for explanation.

as PMNs from normal donors. These results were verified by Goldstein et al[97] using a similar assay and S aureus and E coli opsonized by pooled normal human serum. They showed that bactericidal activity for S aureus and E coli by peripheral blood and peritoneal mononuclear cells from both CAPD patients and healthy controls was similar. (The peritoneal monocytes from healthy controls were obtained from women undergoing laparoscopy.)

To evaluate oxidative metabolism, CL of peritoneal macrophages was measured at rest and in response to opsonized zymosan (particulate stimulus) and PMA (nonparticulate stimulus). Stimulation by zymosan or PMA showed that these cells had only 36% and 32% of the CL response of healthy donor PMNs, respectively. Peritoneal macrophages, however, showed an oxidative burst in response to these stimuli as evidenced by an 11-fold increase in CL over resting values. Although these results were not compared to any normal cells, the uptake of O_2 by peritoneal macrophages was accompanied by an increase in the rate of hexose monophosphate shunt activity.[100]

Peterson et al investigated the interaction of peritoneal macrophages from uninfected CAPD patients with C albicans.[102] Their findings showed a barely detectable CL response of these macrophages to the Candida and they killed only 13% of the organisms. In addition, there were decreased levels of MPO in these macrophages and deficient superoxide production during phagocytosis of the Candida.

Using the chemoattractant fMLP, Goldstein et al[97] found that both monocytes from peripheral blood and the peritoneal cavity of CAPD patients had a significantly higher in vitro chemotactic index than monocytes from the peripheral blood and peritoneal cavity of healthy volunteers. In addition, they found that the chemotactic response of peripheral blood monocytes from HD patients was similar to normal controls. Hydrogen peroxide stimulation in response to PMA showed similar levels of production in peripheral blood monocytes and peritoneal macrophages from both CAPD patients and normal controls.

The opsonic ability of peritoneal effluents has been described in two different studies.[100,101] The concentrations of IgG and C3 were determined in both serum and peritoneal dialysate effluents in CAPD patients. Although the patients' serum concentrations of both IgG and C3 were within the normal range, the peritoneal dialysis effluents from CAPD patients contained only approximately 1% of these important opsonic molecules.[100,101] Normally, peritoneal fluid has IgG and C3 concentrations comparable to that found in serum.[103]

These decreased levels of IgG and C3 suggest that CAPD patients have critical defects in the opsonic activity in the peritoneal cavity. When the opsonic activity of peritoneal effluents was tested, this activity for S epidermidis was approximately 1% of that in normal serum. The opsonic activity of dialysis effluent and serum was primarily heat-stable because heat inactivation did not appreciably alter opsonization of S epidermidis. In contrast to normal serum, the dialysis effluent had no effect in promoting phagocytosis of E coli.[101] This would be an expected finding with the virtual absence of C3 in the dialysis effluent. The previous phagocytosis studies described indicated that phagocytosis of E coli occurs predominately via C3b or C3bi receptors on the surface of peritoneal macrophages. There was a significant correlation between dialysis effluent opsonic activity and dialysis effluent IgG concentration, as measured by percent uptake of S epidermidis by peritoneal macrophages.[104] Although a low IgG concentration was associated with low opsonic activity, a high IgG concentration was not always associated with high opsonic activity, suggesting there are other contributing factors such as antibody specificity for opsonization.

The relationship between opsonic activity and peritonitis was demonstrated in a prospective study designed to correlate levels of heat-stable opsonic activity and IgG concentrations with the incidence of peritonitis.[101] Although there was a wide range of heat-stable opsonic activity in PD effluents among the patients, this activity was relatively constant in each patient. The findings indicated that patients with low opsonic activity had a significantly greater incidence of S epidermidis peritonitis than those with high activity in the peritoneal effluent. The frequency of potential exposure to S epidermidis compared with E coli suggests that the deficiency in opsonic activity against S epidermidis has greater clinical significance.

The results of these studies on host defenses in the peritoneal cavity indicate that there are inadequate numbers of macrophages (per fluid volume) as well as low levels of opsonins. Thus, the current CAPD method removes actively phagocytic

cells and opsonins from the peritoneal cavity and instills fluid that dilutes the number of remaining peritoneal macrophages. These studies suggest that local cellular and humoral mechanisms of defense are inadequate for protection of CAPD patients against peritonitis.

Peripheral WBC Function

A series of studies from this laboratory using peripheral WBC from CAPD patients to evaluate chemotactic receptors, chemotaxis, and chemotactic-factor–mediated functional responses showed that, similar to the HD patients studied, there was decreased availability of C5a receptors on both the peripheral blood PMNs and monocytes of CAPD patients.[49,50] In addition, there were fewer C5a receptor-positive monocytes in the CAPD patients compared with the HD patients. There were no significant differences between CAPD patients and normal controls in the binding of casein to either PMNs or monocytes. Although there was no difference (compared to controls) in the percentage of PMNs that bound fMLPL, there was a decrease in the fMLPL-receptor-bearing monocytes.

It is more difficult to explain the decrease in C5a receptor-positive PMNs in the CAPD patients (compared with HD patients) because they are not exposed to continuous generation of C5a secondary to complement activation of the HD membrane. It may be that the indwelling peritoneal catheter and the continual chemical stimulation of the dialysate solution has an activation effect on the complement system. This complement activation could produce enough C5a to ultimately block the C5a receptors on circulating cells, although evidence for this does not currently exist. Another explanation may be that all CRF patients, regardless of treatment, have decreased C5a-receptor-positive PMNs and monocytes. In the previously cited study by Chenoweth et al[37] they found not only an increase in plasma C5a levels in the HD patients but also in untreated uremic patients. Thus, it may be that the disease itself stimulates continual generation of C5a.

The data we obtained from the monocytes of CAPD patients (as compared to the controls) indicated a much lower percentage of C5a-receptor-positive monocytes as well as a moderate decrease in the fMLPL-receptor-positive monocytes.[49,50] A possible explanation for these findings, compared with the PMN data, is that the C5a- and fMLPL-

positive monocytes may be continually mobilized to the peritoneal cavity and subsequently removed in the peritoneal effluents. Studies on cellular composition of peritoneal effluents have shown that the cellular response of the peritoneal cavity to long-term peritoneal dialysis is largely monocytic.[91,95] A previous study by Alteri and Leonard[104] showed that monocytes that repopulate the circulation following leukapheresis have a reduced chemotactic response to fMLP and C5a. Therefore, it may be that the current CAPD method removes the chemotactic-responsive monocytes, while replacement of monocytes to the circulation may represent immature monocytes lacking the full expression of C5a and fMLP receptors.

When the in vitro chemotactic responsiveness of PMNs from CAPD patients was determined, we found no difference in the random migration between controls and patients. There was, however, a significant decrease in the directional migration of PMNs in response to both C5a and fMLP.[48]

Chemotactic-factor–mediated functional responses were determined by assessing superoxide anion generation, H_2O_2 production, and MPO release.[48] All three of these responses were significantly decreased when C5a or fMLP were used as stimuli. When either PMNs or monocytes were stimulated with PMA, however, there was no difference between the dialysis patients and normal controls. Goldstein et al[97] also showed that there were similar levels of H_2O_2 production in peripheral monocytes in response to PMA.

Although the decrease in chemotactic-factor–mediated responses with C5a as a stimulus would be an expected result since there is down-regulation of C5a receptors, similar findings with fMLP-stimulated responses are not as easy to explain. The decreased responses with fMLP were not as dramatic when compared with C5a, yet they were all statistically significant. Similar to HD patients, these data suggest that PMNs and monocytes from CAPD patients are desensitized to chemotactic factors, including the specific factor (C5a) as well as a nonspecific factor (fMLP).

Previous studies done by Nelson et al[68,106] suggested that while the specific component of chemotactic factor deactivation is due to down-regulation of the receptor for the specific chemotactic factor, the nonspecific components are possibly due to autooxidative reaction, aggregation and in-

creased adherence, and polymerization of micro-filaments and microtubules. The findings in the studies by Nelson et al would explain our results with decreased PMN and monocyte functional responses to both C5a and fMLP. There would be specific desensitization to C5a and nonspecific desensitization to fMLP.

Our results suggest that in addition to down-regulation of the C5a receptor, these patients' PMNs and monocytes are desensitized or deactivated to other chemotactic factor stimuli because there is exhaustion, inhibition, or inactivation of a postreceptor metabolic event critical to the intracellular response.

The phagocytic, bactericidal, and chemotactic in vitro functions of peripheral blood PMNs from both peritoneal dialysis and HD patients has been compared in two different studies.[38,45] Huttunen et al found that phagocytosis of S epidermidis was normal in CAPD patients but significantly impaired in HD patients.[45] The intracellular killing of S aureus was normal in both groups. The chemotactic function of PMNs, however, seemed to be better for CAPD than HD patients when heat-inactivated serum, zymosan, or casein were used as chemoattractants. In contrast, the chemotactic response to S aureus was better in HD patients than in CAPD patients in whom it was significantly impaired when compared with the normal controls or the HD patients.

The findings of Salant et al[38] differed to some extent from those reported by Huttunen et al. The peritoneal dialysis patients in Salant's study were on intermittent peritoneal dialysis (IPD) compared with CAPD in Huttunen's study. In Salant's study, phagocytosis of C albicans was slightly depressed in both IPD and HD patients as compared to the controls, although the majority of patients in these groups had results that fell within the normal range. Although the sera from occasional patients had slightly depressed opsonic activity, the patient groups did not differ from the controls, indicating the sera could function normally for phagocytosis. Bacterial killing of S aureus by PMNs from either group of dialysis patients was similar to the control group. Although a few patients in each dialysis group showed normal PMN chemotaxis to endotoxin-activated normal serum, both groups showed significant depression when compared with the controls. However, the IPD patients had less severe chemotactic defects than HD patients and

many were within the normal range. An additional set of experiments showed that the sera from either group of patients, when activated by endotoxin, were significantly less chemotactic for normal PMNs than control serum.

The results of these studies on peripheral WBC function in CAPD patients indicate that available C5a receptors are decreased on both PMNs and monocytes. In addition, in vitro PMN chemotaxis and chemotactic-factor–mediated responses such as superoxide anion generation, H_2O_2 production, and MPO release are significantly decreased.

DISCUSSION

Although the factors contributing to the increased susceptibility to infection in dialysis patients are multifaceted, a common finding in many studies is that peripheral PMNs and monocytes from both HD and CAPD patients have decreased C5a receptors and decreased chemotactic-factor–mediated responses. In CAPD patients, the commercial peritoneal dialysate solutions adversely affect (at least temporarily) the function of both peritoneal PMNs and macrophages. In addition, in CAPD patients, there are significant defects in the opsonic activity in the peritoneal cavity as well as inadequate numbers and possible functional responsiveness of macrophages. Although it is difficult to attribute the increased incidence of infection in dialysis patients to a single problem, the cumulative effect of a reduction in C5a receptors and functional responses in HD and CAPD patients, as well as the superimposed lack of opsonic activity in peritoneal fluids in CAPD patients, may be a major cause for increased infection in these patients.

Possible treatment strategies to decrease the incidence of infection in dialysis patients can be directed toward the use of HD membranes with less complement-activating ability and enhancement of local defense mechanisms in the peritoneal cavity of CAPD patients. The host defense mechanisms could possibly be augmented by the addition of opsonins (eg, IgG) to peritoneal dialysis solutions. In addition, effective dialysate solutions need to be developed whose chemical composition and pH will have less of an adverse effect on peritoneal macrophage function.

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